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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,261	09/25/2001	Ilse De Canck	IGJ-002	1026

959 7590 06/17/2003

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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,261	CANCK ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicants comments regarding the restriction requirement set forth in the response filed April 4, 2003 are convincing. Accordingly, the restriction has been modified as follows:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-17 and 22-25, drawn to methods and primers for amplifying exon 2, 3 and/or 4 of HLA-A, classified in class 435, subclass 6 and Class 536, subclass 24.33.

II. Claims 1-17 and 22-25, drawn to methods and primers for amplifying exons 2, 3 and/or 4 of HLA-C, classified in class 435, subclass 6 and Class 536 subclass 24.33.

III. Claims 1-17 and 22-25, drawn to methods and primers for amplifying exons 2, 3 and/or 4 of HLA-C, classified in class 435, subclass 6 and Class 536 subclass 24.33.

The inventions are distinct, each from the other because of the following reasons:

Each of the claimed inventions is drawn to distinct polynucleotides and methods of amplifying said polynucleotides. Each of the polynucleotides of exon 2, exon 3 and exon 4 have different nucleotide sequences and different functional properties with respect to their use in diagnostic methods. Because of the differences in their structural and functional properties, the polynucleotides are distinct and unobvious over one another.

Sequence Election

In addition, each of the inventions detailed above each reads on patentably distinct inventions drawn to multiple SEQ ID Numbers. The sequences are patentably distinct from each other, and a further restriction is applied to each invention. Applicant must further elect a single set of primer pairs which amplifying exons 2, 3 and 4 of HLA-A or HLA-B or

HLA-C. Accordingly, Applicant should select a total of 6 primers which amplify the regions which correspond to the elected invention of either group I, II, or III as set forth above. In addition, Applicant must elect 3 single locus-specific target sequence from those target sequences set forth in claim 2, such that each of the elected loci correspond to and are amplified by the set of elected primers. It is noted that for each of the generic claims, the claims will be examined for their full scope. However, each claim that recites a specific primer or loci will be examined only to the extent that they read on the elected species. In response to this Office action, Applicants should clearly indicate which primer pairs are elected and the loci that correspond to each of these primer pairs.

It is noted that nucleotide sequences set forth in the claims are structurally distinct chemical compounds and are unobvious and distinct from one another. These sequences are thus deemed to constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.14. Applicant is advised that this is a restriction requirement and should **not** be construed as an election of species.

Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-III require different searches that are not co-extensive (e.g., a search for primers for amplifying exon 2 of HLA-A would not lead one to all

primers for amplifying exon 2 of HLA-B or HLA-C), examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

In the response of April 4, 2003, Applicants elected to prosecute Group I, claims 1-17 and 22-25, i..e. amplification of exons 2, 3 and/or 4 of HLA-A. Applicant further elected the following primer pairs SEQ ID NO: SEQ ID NO: 144 and 1 for exon 2; SEQ ID NO: 104 and 147 for exon 3; and SEQ ID NO: 205 and 311 for exon 4 and methods which amplify the target positions of 67, 181 and 501.

2. The disclosure is objected to because of the following informalities:

In claim 4, a "." should be inserted following the recitation of "(SEQ ID NO: 309)". See MPEP 608.01(m).

3. Claims 1-9, 12, 15, 16, 17, and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-9 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims recite only a step of hybridizing a primer to a target sequence. The claims do not set forth the steps by which the hybridized primer is extended so as to result in the amplification of exon 2, 3 or 4 of HLA-A.

B. Claims 2-4 are indefinite because the claims reference specific figures but it is not clear as to what portion of the figure is being referred to. For example, the claims recite "intron 2 (Fig. 2)". However, Figure 2 recites multiple sequences and thereby it is unclear as to which intron sequence the claims are referring to. Further, each sequence referred to must be accompanied by a specific SEQ ID No (see under 37 CFR §1.821(d)).

C. Claims 5-7 are indefinite because it is not clear as to whether the claims intend to define the exon which is amplified (e.g., the method of claim 1 wherein exon 2 is amplified and the amplification step is performed using a primer consisting of SEQ ID NO: 144, 145 or 146) or whether the claims only define a primer which may be used if the corresponding exon is amplified (e.g., claim 5 encompasses amplifying exons 2, 3 or 4; if exon 2 is amplified the forward primer consists of SEQ ID NO: 144, 145 or 146 and if exons 3 and 4 are amplified, any locus-specific primer may be used).

D. Claims 12 and 15 are indefinite over the recitation of "the alleles" because it is not clear as to whether the primer hybridizes to intron 3 of each of the HLA-A, HLA-B and HLA-C alleles or hybridizes to intron 3 of only one of the HLA-A or HLA-B or HLA-C alleles.

E. Claims 16 and 17 are indefinite and confusing because the claims improperly depend from 2 claims simultaneously.

F. Claim 22 is indefinite and vague because it is not clear as to whether the claim is intended to be limited to methods of amplifying an HLA-A allele or methods of typing or subtyping an HLA-A allele. The claims are drawn to methods for amplifying HLA-A alleles, yet the final step is one of typing or subtyping HLA-A alleles. Thereby, the final step set forth in the claim is distinct from the objective set forth in the preamble of the claim.

G. Claims 23-25 are indefinite and confusing over the recitation of "or a line probe assay". It is first noted that a claim may not simultaneously be drawn to a both a product and a method. Secondly, if the claims are intended to be drawn to a method, they claims should be amended to include positive, active process steps, see Ex parte Erlich 3 USPQ 2d 1011. The claims omit essential process steps in that the recitation that the assay comprises a primer does not provide and adequate characterization of the steps required to accomplish the line probe assay for typing or subtyping HLA-A.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 5, 6, 10-11, 13, 14, 22, 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Yang (US Patent No. 6,030,775).

Yang (see, for example, columns 4-6) teaches methods for amplifying HLA-A using locus-specific primers and further analyzing the amplified sequences to determine the type or subtype of the HLA-A allele. In particular, Yang teaches amplifying exon 2 and 3 together in a single reaction using one set of primers or amplifying exon 2 and 3 separately using 2 sets of amplification primers. Yang (column 5) states that "It will be appreciated, however, that exons 2 and 3 could be amplified individually by selecting a second amplification primer for exon 2 and a first primer for exon 3 which hybridize with intron 2 (SEQ ID Nos: 2, 5, and 8) ." The reference (column 5, lines 52-54) also states that "(p)referably, both primers will be locus-specific in their hybridization to the HLA gene." Primers are exemplified which hybridize to intron 1 and intron 2 and which amplify exon 2 and primers which hybridize to intron 2 and intron 3 and amplify exon 3 (see columns 4-6). Yang (column 6, lines 2-7) states that "amplification primers which are a few bases longer by virtue of adding additional complementry bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG. 4." Further, additional locus-specific primers within introns 1 and 2 are shown in Figures 2 and 3 (see also column 5). Yang (column 17) also discloses kits containing the locus-specific primers

and primer pairs which specifically hybridize to intron 1, intron 2, intron 3 of the HLA-A gene. Accordingly, Yang teaches a method for amplifying exon 2 using a reverse primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A and methods for amplifying exon 3 using a forward primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A or a reverse primer which specifically hybridizes to a locus-specific sequence in intron 3 of HLA-A.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10, 11, 13, 14, 22, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang.

Yang (see, for example, columns 4-6) teaches methods for amplifying HLA-A using locus-specific primers and further analyzing the amplified sequences to determine the type or subtype of the HLA-A allele. In particular, Yang teaches amplifying exon 2 and 3 together in a single

reaction using one set of primers or amplifying exon 2 and 3 separately using 2 sets of amplification primers. Yang (column 5) states that "It will be appreciated, however, that exons 2 and 3 could be amplified individually by selecting a second amplification primer for exon 2 and a first primer for exon 3 which hybridize with intron 2 (SEQ ID Nos: 2, 5, and 8) ." The reference (column 5, lines 52-54) also states that "(p)referably, both primers will be locus-specific in their hybridization to the HLA gene." Primers are exemplified which hybridize to intron 1 and intron 2 and which amplify exon 2 and primers which hybridize to intron 2 and intron 3 and amplify exon 3 (see columns 4-6). Yang (column 6, lines 2-7) states that "amplification primers which are a few bases longer by virtue of adding additional complementry bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG. 4." Further, additional locus-specific primers within introns 1 and 2 are shown in Figures 2 and 3 (see also column 5). Yang (column 17) also discloses kits containing the locus-specific primers and primer pairs which specifically hybridize to intron 1, intron 2, intron 3 of the HLA-A gene. Accordingly, Yang teaches a method for amplifying exon 2 using a reverse primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A and methods for amplifying exon 3 using a forward primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A or a reverse primer which specifically hybridizes to a locus-specific sequence in intron 3 of HLA-A. Yang does not teach primers which hybridize to a locus-specific target sequence situated at position 67, 181 of HLA-A intron 2 or position 501 of HLA-A intron 3.

However, Yang teaches the sequences of intron 1, 2 and 3 for 13 HLA-A types (see Figure 5) and for several HLA-B and HLA-C types. Yang also teaches a consensus sequence for each of these introns. The alignments provided by Yang identify nucleotide sequences which are conserved and those which are variable. As shown by the alignment of Yang, the sequences at and surrounding positions 67 and 181 of intron 2 and position 501 of intron 3 are conserved amongst the HLA-A types. Further, Yang teaches that locus-specific primers are designed by comparing the sequence alignments set forth in Figures 5A-5H and identifying the conserved sequences (see column 4). Yang also states (column 6) that "(a)s is the case of the first amplification primer, amplification primers which are made a few bases longer by virtue of adding additional complementary bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG.4."

In view of the teachings of Yang, including the teachings of the sequence alignment of introns 2, 3 and 4 of HLA-A, HLA-B and HLA-C and the guidance provided by Yang as to how to select additional locus-specific primers, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional primers, including the primers of the present invention which terminate at positions 67 and 181 of intron 2 and position 501 of intron 3, because such primers would have hybridized to conserved HLA-A sequences and would have provided an equally effective means for separately amplifying exons 2 and 3 of HLA-A. In the absence of unexpected results, primers which hybridize to sequences identified by Yang

as being conserved are considered to be obvious variants of the multitude of primers disclosed by Yang which have the attributes of being locus-specific and useful for individually amplifying exons 2 and 3 of HLA-A. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers in a kit for the convenience of practioners in the art wishing to amplify and characterize exon 2 and 3 sequences.

6. Claims 9, 12, 15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang, as applied to claims 1-4, 7, 8, 10, 11, 13, 14, 22, 24, and 25 above and further in view of Date (Tissue Antigens (1996) 47:93-101) and Schletinga (Human Immunology (1997)57:120-128).

The teachings of Yang are presented above. As discussed above, Yang teaches locus-specific primers which hybridize to intron 3 and teaches that the complements of primers may be used for amplification. Yang also provides an alignment of 13 intron 3 sequences from different HLA-A types, and from different HLA-B and HLA-C types and provides extensive guidance for the selection of additional locus-specific primers that hybridize to intron 3. Yang teaches individually amplifying exon 2 and exon 3 of HLA-A, but does not exemplify amplifying exon 4 of HLA-A.

Date teaches amplifying exon 4 using a reverse primer that hybridizes to exon 4 and determining the sequence of the amplified fragments of exon 4 (see pages 94-95 and Figure 1). Date also teaches that sequences within exon 4 can be used to distinguish different HLA-A types from one another (see pages 98-99).

Scheltinga (page 124 and Figure 1) teaches a primer that hybridizes to sequences within intron 4 and the sequencing of exon 4 using primers which hybridize to intron 3 and intron 4. The reference teaches amplification of exon 4 using a reverse primer that hybridizes to exon 5. Scheltinga also teaches that a polymorphism was identified in exon 4 which is useful in distinguishing between HLA-A types.

In view of the teachings of Date and Scheltinga, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modified the method of Yang so as to have also amplified exon 4 using a forward primer that hybridizes to a locus-specific sequence of intron 3 and a reverse primer that hybridizes to intron 4, such as a primer disclosed by Scheltinga or Yang, in order to have provided amplified fragments of exon 4 that could be sequenced and used to further define the HLA-A type. In the absence of unexpected results, reverse primers for amplifying exon 4 which hybridize to a locus specific region that terminates at position 501 of intron 3 or which consist of the sequence of SEQ ID NO: 205 would have been obvious in view of the teachings of Yang of the alignment of intron 3 HLA-A, HLA-B and HLA-C sequences, which alignment identifies the sequences at position 501 and 5' sequences surrounding position 501 as being conserved amongst HLA-A types and in view of the guidance of Yang for selecting additional locus-specific primers within intron 3. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers in a kit for the convenience of practioners in the art wishing to amplify and characterize exon 4 sequences.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yang, as applied to claims 1-4, 7, 8, 10, 11, 13, 14, 22, 24, and 25 above and further in view of Mullis (US Patent No. 4,683,195).

The teachings of Yang are presented above. In particularly, Yang teaches primer sets for amplifying exon 2 and exon 3. Yang does not teach multiplex primer mixes containing primers for amplifying both exon 2 and exon 3.

However, Mullis (see for example column 10) teaches multiplex amplification methods in which multiple sets of primers are used to simultaneously amplify and detect different target sequences.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modified the method and compositions of Yang so as to have simultaneously amplified exons 2 and 3 using a mixture of primer sets for amplifying exons 2 and 3 in order to have provided a more rapid and efficient means for characterizing HLA-A types.

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yang, Date and Schletinga as applied to claims 9, 12, 15 and 23 above and further in view of Mullis.

The teachings of Yang, Date and Schletinga are presented above. In particularly, the combined references teaches primer sets for amplifying exon 2, exon 3 and exon 4 separately. The combined references do not teach multiplex primer mixes containing primers for amplifying exon 2, 3 and 4.

However, Mullis (see for example column 10) teaches multiplex amplification methods in which multiple sets of primers are used to simultaneously amplify and detect different target sequences.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modified the method and compositions of Yang so as to have simultaneously amplified exons 2, 3 and 4 using a mixture of primer sets wherein the first primer set amplifies exon 2, the second primer set amplifies exon 3 and the third primer set amplifies exon 4 in order to have provided a more rapid and efficient means for characterizing HLA-A types.

9. **PRIORITY**

Acknowledgment is made of applicant's claim for foreign priority based on an application EP 99870068.6 filed 04/09/99 . It is noted, however, that applicant has not filed a certified copy of the EP application as required by 35 U.S.C. 119(b).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER